Cellular histone modification patterns predict prognosis and treatment response in resectable pancreatic adenocarcinoma: results from RTOG 9704.

Journal: J Clin Oncol

Publication Year: 2010

Authors: Ananya Manuyakorn, Rebecca Paulus, James Farrell, Nicole A Dawson, Sheila Tze, Gardenia Cheung-Lau, Oscar Joe Hines, Howard Reber, David B Seligson, Steve Horvath, Siavash K Kurdistani, Chandhan Guha, David W Dawson

PubMed link: 20142597

Funding Grants: Epigenetics in cancer stem cell initiation and clinical outcome prediction

Public Summary:
Histone proteins are the principal components of chromatin and chromosomes, help compact the DNA, and participate in regulation of gene expression that determines a cell's function. Chemical modifications of histones, such as acetylation and methylation, are a mechanism by which histones exert their regulatory effect on gene expression. Histone modification levels differ between different cell types. For example, embryonic stem cells generally have higher levels of histone acetylation than more differentiated cells for reasons that are unclear but are under investigation. Cancer cells also show variability in the levels of histone modifications. We had previously found that the levels of histone modifications in cancer tissues can distinguish indolent versus aggressive forms of cancer. This information could be useful in determining the correct treatment plan for individual patients. In this collaborative study, we show that histone modifications can also distinguish the aggressive forms of pancreatic cancer from the ones that are less so. But more important, histone modifications can predict the response of patients to 5-fluorouracil (5-FU), a chemotherapeutic agent that is commonly used to treat cancer patients. This is the first time that histone modifications have been shown to be predictive of drug response. Therefore, histone modifications levels may help identify cancer patients' responsiveness to 5-FU, enabling the physician to make better informed clinical decisions. While promising, our data need to be validated independently by other laboratories to verify the conclusions.

Scientific Abstract:
PURPOSE Differences in cellular levels of histone modifications have predicted clinical outcome in certain cancers. Here, we studied the prognostic and predictive value of three histone modifications in pancreatic adenocarcinoma. METHODS Tissue microarrays (TMAs) from two pancreatic adenocarcinoma cohorts were examined, including those from a 195-patient cohort from Radiation Therapy Oncology Group trial RTOG 9704, a multicenter, phase III, randomized treatment trial comparing adjuvant gemcitabine with fluorouracil and a 140-patient cohort of patients with stage I or II cancer from University of California, Los Angeles Medical Center. Immunohistochemistry was performed for histone H3 lysine 4 dimethylation (H3K4me2), histone H3 lysine 9 dimethylation (H3K9me2), and histone H3 lysine 18 acetylation (H3K18ac). Positive tumor cell staining for each histone modification was used to classify patients into low- and high-staining groups, which were related to clinicopathologic parameters and clinical outcome measures. Results Low cellular levels of H3K4me2, H3K9me2, or H3K18ac were each significant and independent predictors of poor survival in univariate and multivariate models, and combined low levels of H3K4me2 and/or H3K18ac were the most significant predictor of overall survival (hazard ratio, 2.93; 95% CI, 1.78 to 4.82) in the University of California, Los Angeles cohort. In subgroup analyses, histone levels were predictive of survival specifically for those patients with node-negative cancer or for those patients receiving adjuvant fluorouracil, but not gemcitabine, in RTOG 9704. CONCLUSION Cellular levels of histone modifications define previously unrecognized subsets of patients with pancreatic adenocarcinoma with distinct epigenetic phenotypes and clinical outcomes and represent prognostic and predictive biomarkers that could inform clinical decisions, including the use of fluorouracil chemotherapy.